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Memorandum

To: Dockets Management Branch
Food and Drug Administration

From: Patrick West

Phone:

Date: 10/31/00

Re: Docket # 00N-1380

CC:

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

- **Comments:**

Following is our comment on "Proposed Approach to Regulation of Cellular and Tissue Based Products – Human Bone Allograft Products," docket number 00N-1380. A fax copy has been sent directly to Kathy Eberhart at CEBR.

Also enclosed is a copy of an abstract from the North American Spine Society meeting held this past week addressing some of the specific concerns addressed in our position. As this is very recent data, it was not possible to include it in the body of our document but as it is directly demonstrative of the concerns related to these products, we feel it is important that it be formally included with our position.

00N-1380

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October 31, 2000

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Rockville, Maryland

Re: Docket No. 00N-1380
Comment on Proposed Approach to Regulation of Cellular and Tissue-Based Products—Human Bone Allograft Products

Dear Sir or Madam:

As a party with a direct interest in the tissue product area, we appreciate the opportunity to provide the Agency with our comments regarding the Proposed Approach to Regulation of Cellular and Tissue-Based Products (Proposed Approach), particularly as it applies to human bone allograft products. Stryker Biotech, Inc., as a developer of medical devices, including substitute bone graft products, is an interested party in the development of the regulatory scheme for which FDA now seeks input from industry. We support the Agency's continuing outreach efforts to academia, industry and health care providers in order to achieve some reasonable consensus on the potential regulatory scheme for these important products.

In the Proposed Approach, the Agency stated that the goals of this new regulatory initiative was to address several concerns that it felt were raised by the therapeutic use of cellular and tissue- based products. These concerns included communicable disease transmission, contamination prevention, clinical safety and effectiveness, and labeling/promotion. For the purposes of this comment, we will not focus on all of these goals, but we note, in passing, our general agreement with the Agency that all of these concerns are relevant, certainly in regard to bone allograft products and the new generation of substitutes that now are being marketed or are under development. As set forth in greater detail below, we believe that appropriately tailored regulation of these products, as well as new generations of products, are justified and necessary to ensure that any allograft products being offered for sale to physicians are both safe and effective, and do not pose a risk to public health.

At the outset, we recognize and appreciate the therapeutic contributions that bone allograft products have made to the surgical community and patients alike. The first graft products primarily were developed by surgeons and consisted of bone harvested from

cadavers at their institutions which they then "minimally manipulated" in the operating room by shaping the bone to achieve desired fit at the time of surgery. Over the past several years, the allograft industry has developed so that it can deliver a ready source of graft bone from human donor sources, thereby providing greater access and convenience to both the surgeon and patient. More recently, the allograft industry has grown to include new technologies, including bone graft substitutes, which can be comprised of allograft bone in combination with other extenders or fillers. Another group of products, machined bone products, are comprised entirely of allograft bone but are extensively machined to replicate other FDA-approved devices that are composed of metal, carbon fiber, or other FDA-sanctioned materials. These new technologies raise several important issues, which directly relate to any proposed regulatory scheme FDA now seeks to develop.

The Criteria for Premarket Approval in the Proposed Regulation is Not Appropriate for Human Bone Allograft Products

In the Proposed Approach, the Agency appeared to envision a regulatory system in which products that were, *inter alia*, combined with non-cellular/non-tissue components, more than minimally manipulated, or promoted or labeled for other than a "homologous" use would be regulated under Section 351 of the Public Health Service Act (PHS Act), and possibly under the Federal Food, Drug and Cosmetic Act as a drug or device. In such instances, the resulting tissue-based product was to be subject to <u>some</u> level of premarket review, although it was suggested that the Agency would, for certain products, establish product or class specific controls and standards that would allow product applicants to certify compliance and avoid the need to submit all underlying data for review. However, as described in greater detail below, it appears that the Agency is now on the verge of proposing far less stringent regulatory controls than would appear to be required for this group of highly sophisticated medical products, thus posing a potential public health concern.

<u>Bone Graft Substitutes: Addition of Non-cellular/Non-tissue Components Other Than Drugs and Devices Could Raise Additional Safety and Effectiveness Concerns</u>

In the proposed final rule for establishment registration (64 Fed.Reg. 52696), the Agency abandoned the criteria for regulating tissue-based products set out in the Proposed Approach, opting instead for regulation and premarket approval only for those products that were "combined with or modified by the addition of any component that is a <u>drug or device</u>." 64 Fed.Reg. at 52720 (emphasis added). We believe that this proposal does not provide adequate regulatory oversight for the following reasons.

As a general matter, additional safety and effectiveness questions may be raised regardless of whether the tissue is combined with a drug or device, or with any other

component. We are aware that various bone graft substitutes can be comprised of a small fraction (e.g., less than 25 %) of allograft bone, with the balance of the product being made up of other "excipients" which can be of animal or synthetic origin, but are nevertheless essential to performance of the finished product. In such cases, the excipients only may have been minimally screened (e.g., by animal models or with organic compounds for interaction), which, in turn, may not necessarily characterize the likely behavior of the combined product when it is implanted, *in vivo*. For example, it is well-known that certain compounds can elicit or induce unforeseen physiologic changes, such as cross-linkage at the cell membrane or directly on receptors, and this behavior is not necessarily correlated to a compound acting as a drug or device. However, under the Agency's proposed rule, there would be no premarket review to assess the purported safety profile of such products, particularly those in which various non-bone carriers or delivery materials comprise a significant portion of the final product. Moreover, there are no proposed regulatory provisions for appropriate safety testing, evaluation, or screening for infections agents for these "excipients."

Examples of such products include those made up of demineralized bone combined with the likes of glycerol, which has known toxic effects (see attached), Hyluronic acid, which when implanted by itself is regulated as a class III device and porcine collagen combined with a pluronic handling agent, both of which would be regulated as class III devices if regulated separately.

Another point that should be considered is that often these excipients raise questions regarding whether they truly possess functionality that is integral to overall product performance. In such cases, whether these components, alone, would be subject to some degree of premarket review by the Agency (e.g., 510(k) or PMA) can never be evaluated, and they will not be regulated in any way by FDA under the proposed regulation. Thus, to protect the public health, FDA should have some regulatory criteria for screening these excipients and the products in which they are used.

In function, the proposed regulation focuses solely on the bone or "tissue" component of any product composed of bone and an excipient, and essentially eliminates any ability of the FDA to regulate the resulting product, even if this excipient likely will present a concern over safety and performance. Obviously, FDA will have far more information available to it regarding approved or cleared drugs and devices than it will for the broad category of excipients which can be combined with tissue. However, the practical effect of such a broad definition is that manufacturers will be able to characterize almost a limitless number of components as excipients, each presenting possible safety and performance considerations, with no requirement that they be reviewed by FDA. Absent a more broad-reaching regulation, it is very likely that manufacturers can—and will—use components that will present at least as much of a safety concern as that posed by drugs and devices.

In addition, it is unclear what standards, if any, will apply to the methods used in the manufacture, safety testing, packaging and holding of the tissue-based products which contain excipients. Under the proposed regulation, tissue-based products that incorporate excipients other than drugs or devices would not necessarily be subject to any controls over the safety, quality of product, or manufacturing methods used to produce it. In a practical sense, a substitute bone graft product is not unlike a pharmaceutical or biologic product, in that it contains a primary "active" ingredient (i.e., the allograft bone) and excipients (e.g., fillers or extenders), which are combined together with demineralized bone to yield the finished bone graft substitute product. Such excipients comprise a proportion of the final product composition, and therefore the origin, quality and controls that apply to these excipients will not only have a profound affect on safety but also on the final product performance attributes claimed by the manufacturer.

For purpose of illustration, a given firm could manufacture a substitute bone graft product containing 40% demineralized bone and 60% "excipient" and claim specific performance or indication attributes which, in large part, rely on an "excipient." In this case, because the modifying component is considered an "excipient," FDA would not require premarket approval or clearance of such a product before marketing. Additionally, in the proposed regulation, this substitute bone graft product and its components likely would not be subject to any safety standards or current good manufacturing practice (cGMP) requirements, solely because it is demineralized bone combined with a so-called excipient. Moreover, the true safety and performance attributes that the excipient contributes to overall product performance would be neither reviewed nor regulated by FDA. We suggest that such products containing ANY alien materials should not be treated as "human tissue intended for transplantation," and hence should be regulated by FDA.

In those products where the so-called excipients play a role in defining the characteristics of the allograft bone, then quality standards and controls over the excipients largely will dictate the consistency and reproducibility of the final product. We believe—and think, in the interest of public health that the agency would agree—that the quality and safety of such implanted products, particularly when performance claims are made, cannot be assured absent appropriate quality standards and controls over the excipients used in the product, as well as manufacturing methods used to produce the final product. Indeed, these requirements should be no less important for non-bone excipients used in tissue products than they would be for other currently marketed implantable devices that might incorporate these same excipients.

Perhaps more importantly, many of these same types of products often claim utility for specific clinical indications without any clinical evaluation or study to support these claims. Thus, a tissue-based product can claim almost limitless clinical applications, yet none of these would be subjected to the same standard of clinical proof that the Agency otherwise applies to fabricated or synthetic devices that are intended for the same uses. We do not understand

why the Agency would permit a lesser clinical burden for this specific category of products, solely because such products are comprised, in part, of tissue.

From a practical perspective, any specific performance, consistency, or clinical claims made for such products only can be reliable if the products are manufactured using controlled and validated processes and methods that are compliant with cGMP requirements. Although several independent standards are cited by the tissue industry generally, many of these are directed at disease transmission and donor screening, and do not require the design and manufacturing control requirements that are reflected in the Agency's cGMP regulations. We do not believe that it is possible to claim specific performance attributes, such as osteoinduction, without first assuring that such a claim is valid and supported by appropriate manufacturing standards that will assure reproducible product performance, let alone establish clinical indications without first conducting human clinical studies as are required for non-bone products making similar claims.

For the foregoing reasons, we believe that the Agency needs to establish much clearer boundaries for human bone allograft products, particularly when other carriers, delivery agents, or fillers are used in conjunction with demineralized bone or other human bone products. We therefore request that the Agency reconsider the approach originally articulated in the Proposed Approach, which would call for regulation if products are comprised of non-cellular or non-tissue components.

Machined Products that are More than Minimally Manipulated Could Raise Additional Safety and Effectiveness Concerns .

We acknowledge that tissue banks must, by necessity, utilize certain physical techniques in order to process allograft bone in order to create a product that has the utility desired by surgeons. Such processing methods include initial cleaning, disinfection, and debridement processes, which are then followed by changing the physical configuration of the tissue by cutting, shaping and sizing of the bone so that it will be suitable for implantation. Bone shaping can be achieved by a variety of methods (e.g., sawing; grinding; drilling; etc.), all of which are designed to achieve the overall "fit" of the final bone graft. It is important to note that for the majority of products manufactured over the past decades, the emphasis at tissue banks properly has been upon preventing contamination and preserving the integrity of the tissue.

Although we are aware that tissue banks do follow some standards regarding tissue disinfection and decontamination, we are aware of no standards for product design, manufacturing, quality, or performance that are applied to machined products. For the most basic machined bone uses, we agree that detailed design or performance criteria may not be

necessary. However, for more sophisticated bone-based devices, such as cortical screws, that are intended and marketed to perform a particular function, appropriate design or processing controls that are validated to establish consistent and predictable performance are needed. We are aware that tissue banks often rely upon feedback from surgeons to develop "specifications" for certain machined products, but we are aware of no performance assessments or criteria that have been developed to determine that a substantially machined bone product will perform in conformance with the claims made for it. It is important to note that we are aware of at least one substantially machined bone product, threaded cortical bone dowels, which can be manufactured and implanted in the same fashion as its titanium counterpart. However, although the titanium device is a Class III device, subject to premarket review and the quality system regulations, including design controls appropriate to demonstrate the expected performance of the device, no such requirements apply to the bone-based product, despite equivalent, if not greater, potential risks.

Control over performance of substantially machined bone products can be further complicated by the addition of various excipients, as discussed in the preceding section. For example, tissue banks often add excipients to enhance product handling, yet the degree to which this may impact on safety and product performance will not have been evaluated by the tissue bank or reviewed by FDA.

For the above reasons, we believe that is important that the definition of what is or is not "minimally manipulated" should be considered not only against the typical manipulations that tissue banks have historically performed, but also in terms of the performance claims or other attributes that are relevant to the final product. For ostensibly the same reasons as we set forth in the preceding section, these products similarly should be subjected to some level of premarket review by FDA.

History of Safe and Effective Use for Current Products May Not Be Adequate in the Absence of Reporting Requirements or Appropriate to New Products

We acknowledge that bone allograft has been utilized for decades by the surgical community in its base form. The surgical community apparently is aware of the safety risks that these products present, and is willing to accept that risk given the clinical benefit that can be realized by using these products. Based upon this "ample history of safe use," the opponents of regulation posit that additional controls are unnecessary and overly burdensome. However, we think this premise is flawed for the following reasons.

First, the history of safe use is largely derived from anecdotal experience and uncontrolled studies, in the absence of a mandatory reporting structure that correlates product safety or performance complaints to specific products. Although the tissue industry is quick to point out that complications associated with bone graft procedures (e.g., infections; graft collapse) are rare, in many cases, the earlier cited history of complications, for example,

evidence of infection-free procedures, can be of limited value, since the medical community did not collect data in controlled studies to determine safety, let alone test for specific infection. In other cases, the claimed safety history is based upon results of studies conducted on limited numbers of patients. While we do not mean to imply that safety of these products is purely anecdotal, it is important to recognize the limitations of these types of evidence, particularly when they are used by the tissue industry not only to defend its current practices as adequate, but also to extrapolate and predict the continued safe use of current products as well as products not yet developed.

Second, it is clear that the two main complications of allograft treatment, infection and graft collapse, cannot be quantified because the origin of either type of adverse event is difficult to confine to a single cause, and also because there is no current mechanism whereby such events can be communicated. This is one of the reasons why a central adverse event reporting system is effective because it permits FDA to maintain a database of adverse events correlated to the product. Thus, while we believe that registration and listing of products serves an important initial purpose to permit FDA to obtain requisite knowledge concerning the state of the tissue industry, additional controls that are designed to detect problems and protect the public health are warranted.

Finally, and from a practical perspective, we believe it is clear that any history of safe use cannot take into account the vast array of products available today as well as those that may be introduced in the next decade. We think it important to note that product history for pure allograft products, while probative of that specific group of products, is largely irrelevant to new processes and products yet to be developed in response to needs of the surgical community. Thus, in the absence of a comprehensive regulatory system, any claimed safety of such devices largely will be by inference, as no data will be provided to or reviewed by FDA before marketing is initiated.

Imposition of Regulatory Requirements, if Reasonably Tailored, Will Not Impede Access to Existing and Innovative Products

As discussed above, we are concerned over labeling and promotional claims, particularly with respect to demineralized bone products that are combined with non-tissue components, as well as allograft bone that is substantially manipulated. Although the tissue industry claims that any regulation by FDA in this area likely to be arbitrary and will impede access to important new products, we believe that FDA can fully articulate these principles through an appropriately tailored regulations and guidance documents similar to those that already are established for devices, drugs and biologics.

For the reasons we discussed above, we believe the Agency needs to carefully consider the implications of the addition of non-tissue components, and attempt to refine the term "minimal manipulation" in order to properly define the scope of any regulatory efforts in this area. Assuming that the Agency succeeds in developing these concepts, then the Agency could establish a regulation that classifies various products in keeping with the definitions. For example, 100% bone allograft products and truly "minimally manipulated" products could be considered Class I devices, exempt from any premarket submission requirement, but subject to the Quality System Regulations and adverse event reporting requirements. Then, as suggested in the Proposed Approach, some aspect of premarket approval or 510(k) clearance would apply to products that use other, non-tissue additives or excipients or are more than minimally manipulated. In all instances, products manufactured using such non-tissue additives or more than minimally manipulated tissue should be required to adhere to the same cGMP requirements and tested to the same standards as if they were to be utilized in other implantable devices or drugs.

FDA should provide appropriate guidance that defines, perhaps by example, the various products that would require premarket approval or clearance. This type of product-specific guidance, which should outline the relevant regulatory approval mechanism, might permit manufacturers to cite appropriate industry standards (e.g., Good Tissue Practices) and provide for certification of compliance, thereby allaying the perceived fear that any regulation likely would create additional regulatory burdens. In this way, the regulatory mechanism could provide manufacturers with a means to communicate the various standards currently being followed, while at the same time permitting the Agency to pass on the suitability of these standards.

A key feature for any such regulation or industry guidance for bone allograft premarket submissions must be simplicity, and should rely on appropriate product-specific regulations that set forth the classification and regulatory treatment for these devices in much the same as other medical device products are defined by regulation. The overall regulatory program should, at a minimum, address such concepts as:

1. claims beyond "homologous" use or as otherwise determined in an applicable regulation;

2. submission requirements to provide clinical proof for such additional performance, clinical, or induction claims;

3. certification to standards or submission of standard in application as an alternative to data submission;

4. the applicability of cGMP, as codified in the Quality System Regulation to:

- component and excipient manufacturers; and

- final product design and manufacturing activities;

5. the applicability of adverse event reporting obligations.

We believe that this type of regulatory approach will permit FDA to evaluate the complexity of newly developed products, while at the same time providing fixed standards that will ensure reliable and safe performance of existing products. As with other regulatory initiatives instituted by FDA over the past years, after a significant body of experience with these devices is gained, then it would be possible to relax or possibly exempt certain products from premarket submission requirements if they are later determined to pose little or no risk. However, we believe that appropriate quality standards and premarket controls are desirable, if not essential, for all products that incorporate additives, are more than minimally manipulated, particularly when specific performance claims are made.

Conclusion

In sum, we believe that appropriate regulatory review of bone based products which include additives, are significantly manipulated, and / or make performance or indication claim is warranted to safeguard the public health. It is in fact only reasonable to expect that a regulatory scheme should be designed to establish appropriate manufacturing standards and review criteria for products which industry actively promotes and are implanted into United States citizens over 250,000 times a year.

Very truly yours,

Jamie Kemler
President, Stryker Biotech

cc: Kathy A. Eberhart, CBER, OCTMA, HFM-49

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North American Spine Society

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gery and were treated nonoperatively with spinal extensor muscle strengthening exercises, medications, and restricted duty. The average follow-up time was 14 months (range 6-24 months). All servicemen completed a functional outcome questionnaire (AAOS/SRS) with emphasis on levels of pre and post treatment function, pain, and satisfaction. The two groups were also evaluated using military physical training (PT) test scores before and after treatment, # of servicemen returning to full, unrestricted military duty after treatment, # of military back pain disability discharges, and the total post-treatment length of time on duty restriction profiles.
Results: 4/14 (29%) of the servicemen managed nonoperatively ultimately received a disability discharge from the military for back pain, another 5/14 (36%) remained on permanent duty restriction profiles, and 5/14 (36 %) returned to full, unrestricted military duty. In the PLIF group, 12/15 soldiers (80%) were able to return to full duty, 3/15 (20%) remained on permanent restrictive duty profiles, and 0/15 (0%) received a disability discharge from the military for back pain. 12/15 (80%) of the PLIF group and 8/14 (57%) of the nonop group were physically able to complete the post treatment military physical fitness test. No difference was observed between premorbid and post-treatment PT test scores in either group. However, scores for patient-assessed post-treatment pain, function and satisfaction were significantly higher in the PLIF group. Soldiers who were able to return to full military duty (n=12 PLIF, n=5 nonop) were able to do so at an average of 4 months post-treatment (range 2-8 months). Complications in the PLIF group included dural tear (n=2), unilateral transient lower extremity paresthesia (n=1) and wound seroma requiring reoperation (n=1).
Conclusions: Instrumented PLIF surgery performed in active duty U.S. servicemen with chronic back pain and single level lumbar disc degeneration results in a high rate of return to full military duty. Servicemen treated with this technique are less likely to receive a back pain disability discharge or a permanent physical limitation profile when compared to servicemen treated nonoperatively. Outcomes with respect to post treatment pain, function, and satisfaction are excellent in those servicemen who are able to return to unrestricted duty.

AN UNEXPECTED OUTCOME DURING TESTING OF COMMERCIALLY AVAILABLE DEMINERALIZED BONE GRAFT MATERIALS

Mathias P.G. Bostrom, MD; X. Yang, MD, New York, NY; M.E. Keenan; Harvinder S. Sandhu, MD; Joseph M. Lane, MD, New York, NY

Purpose: Over the last decade, several different commercially available processed demineralized bone matrix grafting materials have become available for human use. However, there have been no side-by-side comparison of "off the shelf" versions of these products with regard to their ability to form bone in vivo. The purpose of this study was to perform this comparison with commercially available materials in an established animal model.
Material and Methods: Six different types of bone graft materials obtained from our operating room inventory were placed subcutaneously and intermuscularly in

athymic homozygous rats. The bone graft volume used was 1 cc at each site. At the time of sacrifice, the newly formed bone nodules were dissected from the surrounding tissue and high resolution faxitron radiographs were obtained. Samples were analysed for undemineralized histomorphometric analysis. The internal organs of the animals were also removed for pathological analysis.

Results: During the initial two post operative days 8 of the 19 animals on died. All animals that died had received Grafton™ Gel or Putty. Of the 9 animals receiving the Grafton™ materials (either Gel or Putty), 8 died ($p<0.001$). The mean dose of the Grafton™ material was 8.6 ± 0.7 cc/kg. The animals whose deaths were observed demonstrated hematuria prior to expiring.

The high mortality rates prompted the initial experiment to be halted. The protocol was reviewed and revised to implant 0.25 cc at each site instead of the original 1 cc. The remaining 11 animals were implanted with the lower volume. Of this second group, 2 of the 6 animals receiving the Grafton™ materials expired with hematuria prior to death. The mean dose of Grafton™ implanted in this second experiment was 1.6 ± 0.2 cc/kg.

None of the animals implanted with any other bone matrix product (Opteform™, Osteofil™, Dynagraft™ Gel and Putty) died. Three different lots of Grafton™ Gel and Putty, manufactured on different days, were used. Histologic analysis of the kidneys in all the rats that died demonstrated evidence of acute tubular necrosis with some glomerular hemorrhage. These findings were consistent with an acute toxic reaction.

Discussion: The results after the use of Grafton™ in this study were unexpected. While the exact cause of death remains unclear, histologic analysis appears to implicate an acute toxic reaction causing acute tubular necrosis and subsequent death. It appears that the glycerol in the Grafton™ may be responsible. Glycerol has been implicated in renal toxicity and there is a well established glycerol-induced acute renal failure model in the rat. Although the results of this preliminary investigation may have no clinical implication in healthy patients implanted with lower doses of Grafton™, we feel that glycerol containing bone matrix products must be used with extreme caution in lower weight pediatric patients and those at risk for renal disease.

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